REMARKS

Sequence Listing

The enclosed paper copy and computer readable form of the Sequence Listing are submitted in response to the Notice to Comply with Requirements for Patent Applications containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures mailed on February 11, 2003.

The amendments to the specification function to insert the sequence listing and appropriate sequence identifiers into the text of the present application to comply with 37 C.F.R. §1.821 to 1.825.

This Sequence Listing conforms to the requirements of 37 C.F.R. §1.823(b). The Statements required by 37 C.F.R §1.821(f) and (g) are set forth below.

Pursuant to 37 C.F.R. §1.821 (g), the undersigned hereby states that this submission, filed in accordance with 37 C.F.R. §1.821 (g), does not contain new matter.

Pursuant to 37 C.F.R. §1.821 (f), the undersigned hereby states that the content of the paper and computer readable copies of the Sequence Listing submitted in accordance with 37 C.F.R. §1.821 (c) and (e), respectively, are the same.

Restriction Requirement

The Office Action required restriction from among:

Group I: Claims 1-11 and newly added claims 19-21, 25-26, 28-30 and 33-34, drawn to a method for producing a lymphocyte or APC having tolerance to an allergen or an antigen, comprising incubating a lymphocyte or APC with a composition capable of upregulating expression of an endogenous Notch or Notch ligand and the allergen or antigen, classified in class 435, subclass 325;

Group II: Claims 13-16, drawn to use of a composition capable of upregulating expression of an endogenous Notch or Notch ligand in an APC or lymphocyte in a method of producing regulatory lymphocytes capable of suppressing the activity of other lymphocytes, classified in class 435, subclass 7.24;

Group III: Claims 12, 17 and 32, drawn to a method of treating a patient suffering from a disease characterized by inappropriate lymphocyte activity comprising administering a lymphocyte produced by methods of Group I, classified in class 424, subclass 184.1; and

Group IV: Claims 18 and 22-31, drawn to a method for producing a lymphocyte having tolerance to an allergen or an antigen comprising incubating an APC with a lymphocyte, classified in class 435, subclass 325.

Group I, claims 1-11, 19-21, 25-26, 28-30 and 33-34, is elected with traverse. Applicants retain the right to file divisional applications to non-elected subject matter. Reconsideration and withdrawal of the restriction requirement are respectfully requested in view of the remarks herewith.

The present claims represent a web of knowledge and continuity of effort that merits examination in a single application. Indeed, the claims of all groups are related because they are all drawn to methods for preparing antigen presenting cells (APC) and lymphocytes that can suppress the activity of immune cells, and the use of compositions that upregulate Notch or Notch ligand in these methods.

In this regard, the Examiner's attention is respectfully directed to MPEP § 808.02 which states, ". . . restriction is not required unless one of the following reasons appears:

1. Separate classification;
2. Separate status in the art; or
3. Different field of search . . ."

Contrary to the guideline provided by the MPEP, Groups I, II and IV are in the same class, with Groups I and IV in the same subclass. Further, there is no evidence presented in the Office Action to demonstrate that the claims of the four Groups have acquired separate status in the art. Importantly, the claims in all four Groups involve the upregulation of the expression of endogenous Notch or Notch ligands in APC or lymphocytes, thereby encompassing the same field of search. Thus, restriction is not appropriate.

Additionally, the Examiner's attention is further directed to the text of MPEP § 803 which in part states:

> If the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits ...

A search of the Group I claims will necessarily involve a search of the non-elected groups, particularly Group IV, which is classified in the same class and sub-class, and should therefore be rejoined to elected Group I.

The Office Action also required the election of a specific Notch or Notch ligand. Delta is elected with traverse. It is respectfully submitted that there is no basis for a restriction of this nature, since neither Notch nor Notch ligand is necessarily required in the claimed methods. The invention relates to use of a composition that is capable of upregulating expression of a Notch or Notch ligand. Since such a composition could affect the activity of any Notch or Notch ligand, is submitted that the upregulation of Delta, for example, would not be patentably distinct from the upregulation of Serrate if the activity is being modulated by the same composition.

The Office Action also required the election of a specific composition. IL-10 is elected with traverse. The allegation on page 3 of the Office Action that the species are distinct because "each of said species has a distinct structure with distinct biochemical properties which are conferred by said distinct structure" is not relevant in this instance. The species all have the common property of being capable of upregulating expression of an endogenous Notch or Notch ligand (see claim 1, for example), and are therefore not distinct.

Finally, the Office Action required the election of a specific cell in each case of the recitation of "lymphocyte or antigen presenting cell". It is respectfully submitted that there is no basis for a restriction of this nature, since both species have the common property of being capable of suppressing an immune response in a mammal to the allergen or antigen. That being said, Applicant elect, with traverse, the embodiment of the invention which involves the modification of antigen presenting cell (APC) function such that APCs induce lymphocytes (T cells) to be suppressive. Thus, in claims 1, 19, 21 and 33, for example, Applicants elect lymphocyte for the first occurrence and APC for the second and third occurrences. Applicants elect lymphocyte for the first occurrence and APC for the second occurrence in claim 2, and APC for claim 4. In claims 10 and 30, Applicants elect lymphocyte for the first and second occurrences and APC for the third occurrence.

MPEP 808.01(a) states (in bold print), "[e]lection of species should not be required if the species claimed are considered clearly unpatentable (obvious) over each other."

It is Applicants' understanding that, upon the allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all of the limitations of an allowed generic claim, as provided by 37 C.F.R. 1.141. It is also understood that the Examiner can broaden the search to include other

species, e.g., upon determining that a species is allowable, or as discussed herein, when there is a relationship among the species and/or number of species is not too great.

In this regard, M.P.E.P. § 808.01(a) states that "where there is no disclosure of relationship between species (*see* M.P.E.P. §806.04 (b)), they are independent inventions and election of one invention" is required. In view of M.P.E.P. §803, however, when the generic claim includes sufficiently few species that a search and examination of all the species at one time would not impose a serious burden on the examiner, then a requirement for election is inappropriate. Moreover, MPEP 803.02 specifically provides that members of a claimed *Markush* group must be searched and examined together, if they are not too many in number.

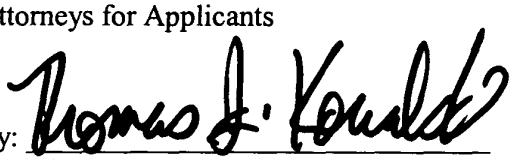
Examination of the generic claims, without election, does not impose a serious burden on the Examiner. An examination of claims wherein the cytokine is IL-10, for example, would inevitably encompass a search that included IL-4, IL-13 and the other recognized members of that group. In addition, the function of APCs and lymphocytes in the instant invention is substantially similar such that any search encompassing one cell type will inevitably include the other. No election should therefore be required.

The result of the present restriction requirement are inefficiencies and unnecessary expenditures by both the Applicants and the PTO and extreme prejudice to Applicants (particularly in view of GATT, a shortened patent term may result in any divisional applications filed); and restriction has not been shown to be proper, especially since the requisite showing of serious burden has not been made in the Office Action and there are relationships between the claims of all nine Groups. Indeed, the search and examination of each Group is likely to be co-extensive and, in any event, would involve such interrelated art that the search and examination of the entire application can be made without undue burden on the Examiner. All of the preceding, therefore, mitigate against restriction.

In view of the foregoing, reconsideration and withdrawal of the restriction requirement and favorable examination of the pending claims on the merits are respectfully requested.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP
Attorneys for Applicants

By: 

Thomas J. Kowalski
Reg. No. 32,147
Tel (212) 588-0800
Fax (212) 588-0500

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

On page 23, line 10:

The sequence of the "forward" Serrate-1 primer is:

5'-GGCTGGGAAGGAACAACCTG-3' (SEQ ID NO:1)

The Serrate- "reverse" primer is:

5'-GGTAGCCATTGATCTCATCCAC-3' (SEQ ID NO:2)

Primers specific for Delta are:

5'-GATTCTCCTGATGACCTCGC-3' (SEQ ID NO:3)

5'-GTGTTCGTCACACACGAAGC-3' (SEQ ID NO:4)

PCR samples were analysed by gel electrophoresis.

Determination of Notch, Serrate and Delta Expression

In the Examples 8-11 the following primers were used as indicated:

Murine Notch1 Accession No. Z11886

Forward primer (FP) 5'-TGTTAATGAGTGCATCTCCAACCC-3' (SEQ ID NO:5)

Reverse primer (RP) 5'-CATTCGTAGCCATCAATCTTGTCC-3' (SEQ ID NO:6)

Murine Notch2 Accession No. D32210

FP 5'-CAGAGGAATAGCAAGACGTGCAAG-3' (SEQ ID NO:7)

RP 5'-GATGAAGAACAGGATGATGACAACAG-3' (SEQ ID NO:8)

Murine Notch4 Accession No. U43691

FP 5'-CTACTGCCACAAGTAGCTGG-3' (SEQ ID NO:9)

RP 5'-CTCGGAGATAGCGTGACTGG-3' (SEQ ID NO:10)

Murine Serrate1 (Jagged1) Shimizu *et al* 1999

FP 5'-GGGGGTCACTGTCAGAATGA-3' (SEQ ID NO:11)

RP 5'-AGATATACCGCACCCCTTCAG-3' (SEQ ID NO:12)

Murine Serrate2 (Jagged2)

FP 5'-ATCTGCGAGGACCTGGTGGAT-3' (SEQ ID NO:13)

RP 5'-TATACCAGAGGGTGCGACA-3' (SEQ ID NO:14)

Murine Delta1 Accession No. X80903

FP 5'-GACTCTCCCGATGACCTC-3' (SEQ ID NO:15)

RP 5'-GATGCACTCATCGCAGTAG-3' (SEQ ID NO:16)